At the wound's edge

Tissue repair is a homeostatic response that involves a wide array of cellular and molecular events. Interestingly, wounding hastens skin carcinogenesis in mouse models. Type II keratins 6a and 6b are induced in epidermal keratinocytes after skin wounding, although ablation of these genes in keratinocytes results in increased migration. Rotty and Coulombe recently examined the role of these structural proteins and the nonreceptor tyrosine kinase Src (which plays a role in cell migration) in wound healing. The increased migratory phenotype of K6-deficient cells resulted from activation of Src kinase and Src substrates that facilitate cell migration. K6 was found to bind to Src dynamically in the detergent-resistant membranes, known sites of Src regulation. Thus, K6 functions in the regulation and optimization of epithelial migration during wound healing via dampening of the activation of Src in wound-activated keratinocytes at the leading edge. (*J Cell Biol* 197:381–9, 2012) *Selected by S. Yuspa*

MicroTuning

Distinct $CD4^+$ T-cell subsets, including T helper type 17 (Th17) cells and natural and induced regulatory T cells (nTregs and iTregs), are thought to exhibit plasticity, and the roles of microRNAs (miRNAs), which are involved in this T-cell plasticity decision via regulation of gene expression at the posttranscriptional level, remain an area of intense investigation. Recently, Takahashi and colleagues found that miR-10a, which is highly expressed in nTregs, is induced by retinoic acid (RA) and transforming growth factor-β and influences the plasticity of these cells. This miRNA directly targets expression of the transcriptional repressor Bcl-6 and the corepressor Ncor2 and ultimately constrains conversion of iTregs to follicular Th cells. Furthermore, miR-10a inhibits Th17-cell differentiation in a manner dependent on induction of the transcription factor T-bet by RA. This factor therefore contributes to maintenance of the Treg phenotype by targeting factors that favor plasticity. Moreover, regulation of miR-10a may be useful to fine-tune factors that influence the stability-versus-plasticity decision in Th cells. (*Nat Immunol* 13:587–95, 2012) *Selected by M. Amagai*

Reconfiguration of memory

A recent randomized controlled trial demonstrated that rituximab, the chimeric mouse–human IgG1 monoclonal antibody that targets CD20 on B lymphocytes before differentiation, can provide long-term benefits to a subset of patients with anti-myelin-associated glycoprotein (anti-MAG) neuropathy, an autoimmune disease of the peripheral nervous system mediated by MAG-specific IgM autoantibodies. Maurer and colleagues found that the long-term immunomodulatory effects and clinical disease remission following treatment with rituximab, which has received approval from the US Food and Drug Administration for a variety of autoimmune conditions, were mediated by the dramatic reduction of expanded autoreactive IgM memory B cells, highlighting a reconfiguration of B-cell memory. The presence of oligoclonal expansion in the IgM memory B-cell compartment before treatment, the ability of these immune cells to recognize MAG antigen, and the persistence of these cells in patients with stable or worsened disease after rituximab treatment allowed nonresponders to be separated from clinical responders. Thus, MAG-specific IgM memory cells are important for the pathogenesis of this autoimmune neuropathy. (*J Clin Invest* 122:1393–402, 2012) *Selected by J. Stanley*

New field guide

Analysis of squamous cell carcinomas led to the notion of field cancerization because frequent tumor multiplicity and changes to epithelial and mesenchymal changes are observed beyond the neoplastic area. Hu and colleagues demonstrated that loss of the *CSL/RBP-Jκ* gene that encodes the Notch signaling effector CSL in mice resulted in stromal atrophy and inflammation, which are potent triggers of epithelial tumors. These mice exhibited features reminiscent of field cancerization: multifocal tumors, expanded alterations of surrounding epithelium, and atrophic changes in the underlying stroma. Similar genetic and cellular changes were observed in human skin samples, indicating potential clinical significance. Importantly, treatment of the *RBP-Jκ* mutant mice with an immunosuppressant COX-2 inhibitor led to delayed formation of focal lesions and tumors, suggesting that inhibition of inflammation may be used to prevent or retard secondary tumor development even in patients with field cancerization. (*Cell* 149:1207–20, 2012). *Selected by B. Gilchrest*

Carcinoma intercept

Basal cell nevus syndrome is characterized by the presence of hundreds to thousands of basal cell carcinomas (BCCs). Patients with this syndrome harbor a defective copy of the Hedgehog inhibiting tumor-suppressor gene *PTCH1*, and essentially all their BCCs exhibit enhanced Hedgehog signaling. This year, the US Food and Drug Administration approved the use of the low-molecular-weight Hedgehog signaling inhibitor vismodegib for treatment of locally advanced or metastatic BCCs. Pursuing a different indication, Tang and colleagues enrolled 41 individuals with basal cell nevus syndrome in a randomized, double-blind, placebo-controlled trial of this drug. Vismodegib significantly reduced the appearance of new surgically eligible BCCs in these patients and also decreased the initially substantial burden of these BCCs. Although the drug was effective, nearly 54% of the patients discontinued vismodegib because of mild or moderate adverse effects. The authors concluded that these results are consistent with the concept of cancer interception, which involves the blockade of further tumor growth before the lesions become clinically apparent. (*N Engl J Med* 366:2180–8, 2012) *Selected by B. Gilchrest*

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